McKinsey&Company

McKinsey Cancer Center
The next wave of innovation in oncology

September 2016

Authored by:
Björn Albrecht
Philippe Menu
Jeff Tsao
Kevin Webster

Oncology today

A new wave of therapeutic and diagnostic technologies in oncology is making its way from the bench to the clinic. While many of these have the potential to transform oncology treatment in the future, manufacturers, regulators and care providers must address a number of topics to deliver on the promise of these technologies. These include among others clinical, regulatory and market access hurdles, but also broader implications for health systems as a whole.

Oncology is experiencing a tidal wave of innovation that may profoundly change how cancer is diagnosed, treated, and monitored in the future, but continues to be a significant unmet medical need. Eight million people die each year of cancer, and its management puts a huge strain on healthcare systems. The annual global cost of cancer drug spend was $107 billion in 2015, and is expected to be around $160 billion in 2020.

Oncology is a key driver of growth for the pharmaceutical industry. It is expected to account for about 30 percent of its product pipeline and 25 percent of pharmaceutical-industry revenue by 2020. However, leading in oncology is difficult. A unique capacity for innovation and risk taking is required. Recent successes in CD38-targeting therapies in multiple myeloma, PARP inhibition in ovarian cancer, and anti-PD-1/anti-CTLA-4 combinations in melanoma are offset by failures and underwhelming results in other areas.

Looking broadly across the industry, we identify the following five major forces at play that will likely shape the future of oncology:

1. Smaller patient populations due either to a focus on niche tumors or narrower stratification of subpopulations in more common tumor types

2. Shorter product life cycles, reduced by almost fivefold since the 1990s because of a more competitive landscape and faster innovation cycles

3. New age of combination therapy and sources of innovation triggered by a recent wave of immuno-oncology launches that have increased the level of external sourcing of innovation and collaboration especially among pharmaceutical and biotechnology companies

4. Significant shift in value across healthcare, partly driven and informed by big data, which in turn will enable more innovative access models

5. New wave of technologies, providing tools to address a broader set of indications and offering greater promise of personalized therapies

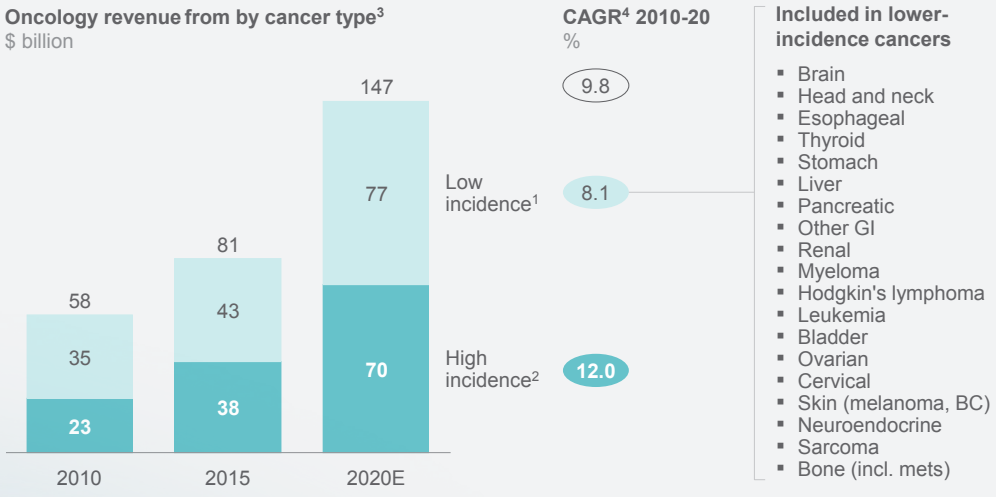
Five forces shaping the future of oncology

1. Smaller patient populations

Current trends in product pipelines indicate that lower-incidence tumors will account for nearly 50 percent of revenue by 2020 (Exhibit 1). This reflects a shift in focus away from high-incidence tumors (for example, lung, colorectal, breast, and prostate) to niche tumors with greater unmet medical needs. Target patient populations are narrowed further by more sophisticated stratification strategies. Nearly half of current Phase III trials conducted by the top ten oncology companies include a companion diagnostic. Ninety percent of biomarkers are used for patient stratification. PD-L1 expression, a putative marker for PD-1/PD-L1 inhibitors, is an exception and is mainly used for retrospective analysis due to a lack of consensus around the assays and the analysis. The move toward narrower indications has important implications for both market access and the go-to-market model, as it requires a shift in focus and capabilities, such as patient finding.

Exhibit 1

Lower-incidence tumor types are expected to account for >50% of sales by 2020



1 Less common cancers are those with incidences less than 30,000 patients that are treated with pharmaceutical therapies. Includes 49 indications
2 Lung, colon, breast, prostate, and non-Hodgkin's lymphoma
3 Excludes supportive care revenue
4 Compound annual growth rate

Source: EvaluatePharma® 2015

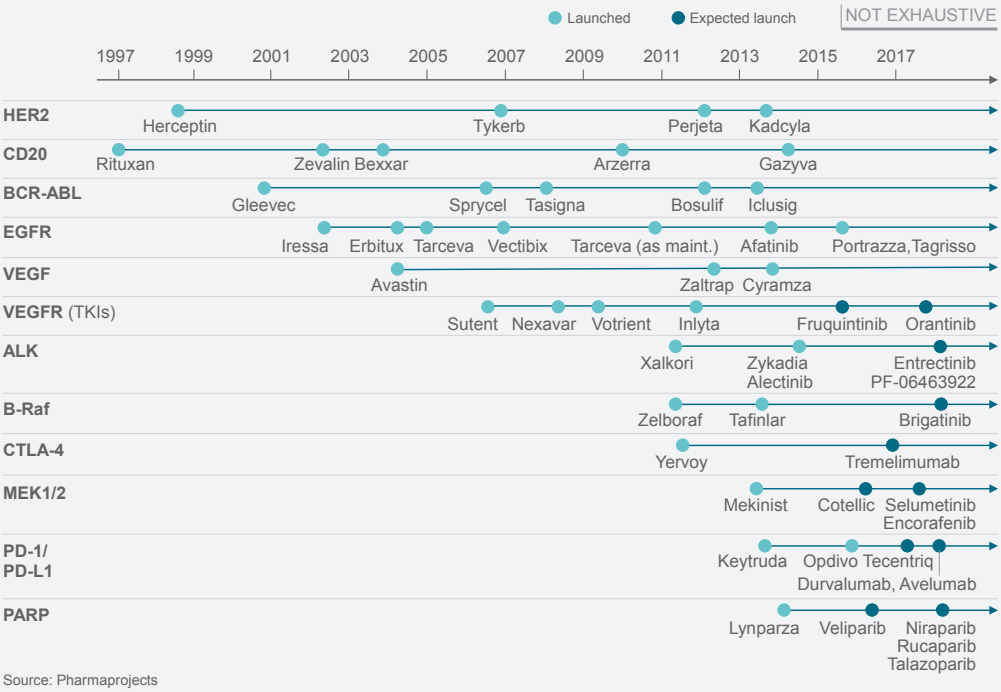
2. Shorter product life cycles

Innovation is a key driver in oncology. Over the last 15 years, novel drugs generated more value in oncology than in any other therapeutic area. However, research and development is concentrated on a minority of potential targets, thereby increasing competitive intensity. Based on our own analyses, 80 percent of the pipeline activity of the top ten oncology companies is focused on 37 percent of all the targets being explored. And 80 percent of compounds in development have at least one competitor in the pipeline.

This intense competition has shortened product life cycles. While Avastin, Gleevec, and Herceptin enjoyed long periods of exclusivity, MEK, PD-1/PD-L1, and PARP inhibitors offer a good indication of how competitive drug development has become (Exhibit 2). An important implication for pharmaceutical companies is that they require agile development capabilities, and regulators must cater to a faster pace of innovation while upholding satisfactory approval standards. The neck-to-neck development of nivolumab and pembrolizumab is a good example of the speed and organizational commitment required for success in highly competitive therapeutic targets.

Exhibit 2

Product life cycle has shortened by almost fivefold from HER2 to now



Source: Pharmaprojects

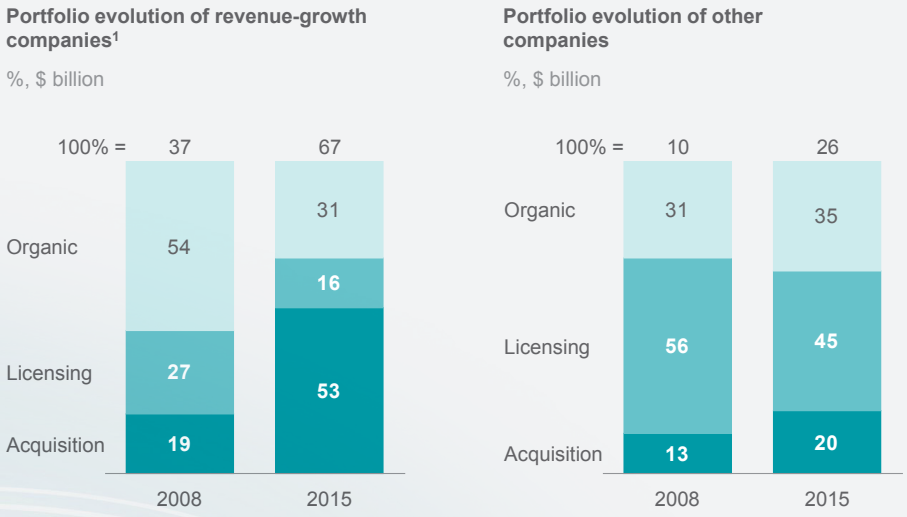
3. New age of combination therapy and source of innovation

Immunotherapies have turbocharged combination opportunities. In the ten most common tumor types, approximately 40 percent of ongoing PD-1/PD-L1 studies involve combinations. This trend toward combination therapy is likely to continue in order to improve efficacy and will include more complex combinations such as triplets. One interesting view is that PD-1/PD-L1 therapies are increasingly expected to become interchangeable backbones, and partner therapies will eventually drive the next wave of value creation.

Combination therapies are just the latest development increasing the external focus and need for collaboration in oncology. In fact, companies that have outgrown the market for at least three consecutive four-year periods, referred to as revenue-growth companies, are characterized by a greater reliance on external innovation in the past 8 years (Exhibit 3). This change is driven not only by an increase in the number of acquisitions but also by an increase in the value of such deals. Interestingly, non-revenue-growth companies are not as active in acquisitions, and have retained approximately the same proportions of internal and external innovation in the same period.

Exhibit 3

Revenue-growth companies focus on inorganic growth



1 Revenue-growth companies: companies that consistently outgrew the market for more than 12 years

Source: EvaluatePharma® 2015

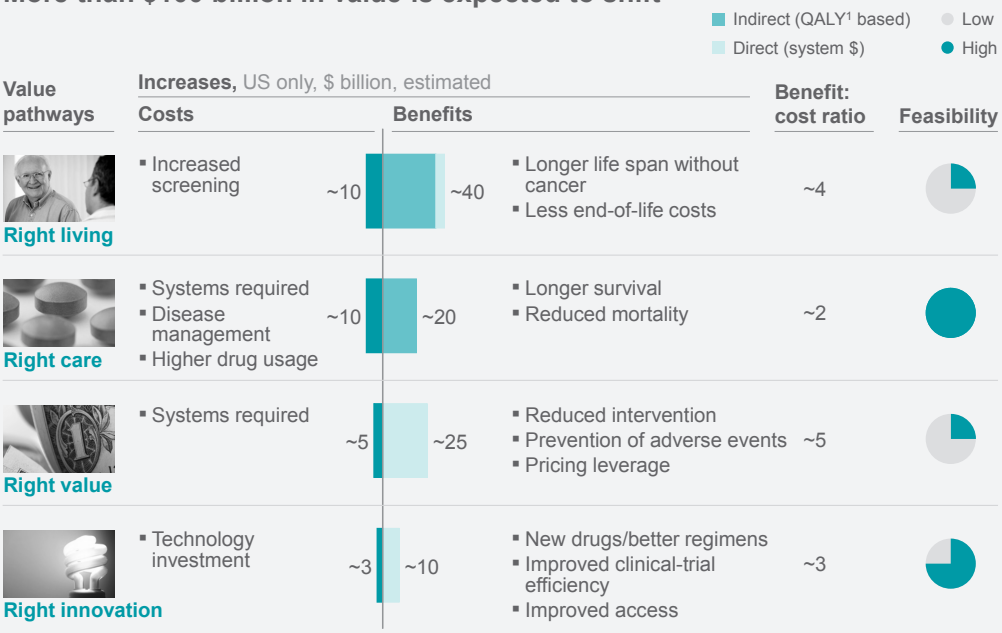
4. Significant shift in value across healthcare

Payors and professional associations are increasingly focused on oncology, partly due to the increasing cost of oncology drugs. Both US payors and health systems outside the US are experimenting with different care models. Payors are graduating from multiple small experiments to preferred models driven by value. For example, the UK National Health Service and Singapore are exploring indication-based approaches that drive cost reallocation to interventions with the greatest benefit in outcomes.

From a system's perspective, and based on our own analysis, more than $100 billion of value in the healthcare system is estimated to shift along specific pathways, resulting in a higher standard of living, better quality of care, more efficacious treatments, and improved access (Exhibit 4). The bulk of the benefits is achieved through better screening and care delivery, resulting in longer cancer-free life span and lower end-of-life cost. New drugs and better regimens are expected to deliver more modest benefits in terms of value, but they also only require a minor increase in health-system costs.

Exhibit 4

More than $100 billion in value is expected to shift



1 Quality-adjusted life-year

Source: McKinsey analysis

Big data will be a key enabler of this shift in value. Real-world evidence and other data sources, such as wearable health devices and electronic health records, will play a central role in providing insights into improving care and allocating health-system spend to optimize outcome for patients.

5. New wave of technologies

A wave of innovation is moving through the industry pipeline. In the late pipeline, this is most pronounced for monoclonal-antibody derivatives such as antibody-drug conjugates and bispecific antibodies. Earlier in the pipeline, advances in cell therapy and nucleic-acid-based therapies are prominent. The move toward personalized therapies with advances in diagnostics like liquid biopsy enables a more nuanced understanding of disease state and treatment response.

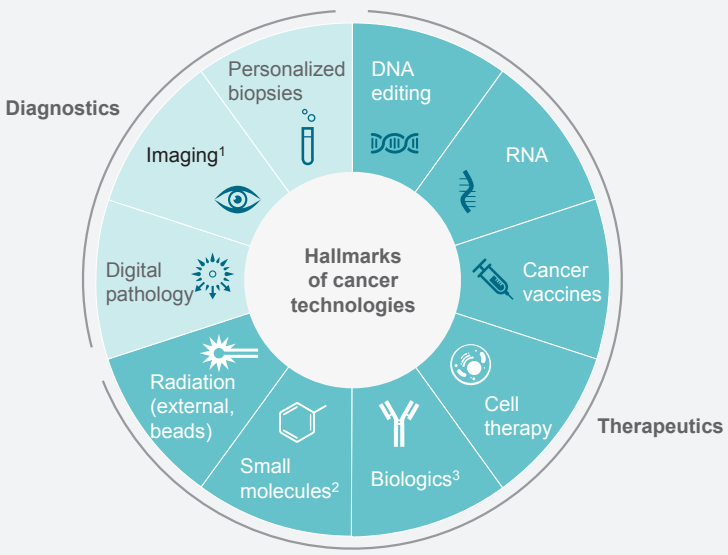
In 2011, Douglas Hanahan and Robert Weinberg published an update to their seminal article "The hallmarks of cancer," which has been cited more than 20,000 times. This paper provided a framework to organize and think about cancer therapies in terms of the specific characteristics of cancers that they address. In the same spirit, we can think of innovation in terms of hallmarks of cancer technology (Exhibit 5, opposite) and group innovation into diagnostic technologies and therapeutic technologies. Diagnostic technologies range from digital pathology and imaging to personalized biopsies. Therapeutic technologies range from nucleic-acid-based approaches (including vaccines) and cell therapies to classic approaches based on small and large molecules, their derivatives, and radiation. Innovation that will affect cancer care in years to come is under way across the entire wheel.

In this context, there are three key questions to consider:

- What are the opportunities created by this new wave of innovation?
- What are the challenges to resolve in order to affect the practice of oncology at scale?
- What will oncology look like in 2025?

Exhibit 5

We organize new therapeutics and diagnostics by the "hallmarks of cancer technologies"



1 Conventional and molecular imaging
2 Including radioactive chemical entities and nanoparticle-encapsulated small molecules
3 Includes antibody-drug conjugates with cytotoxic and radio-isotope payloads

Source: McKinsey analysis

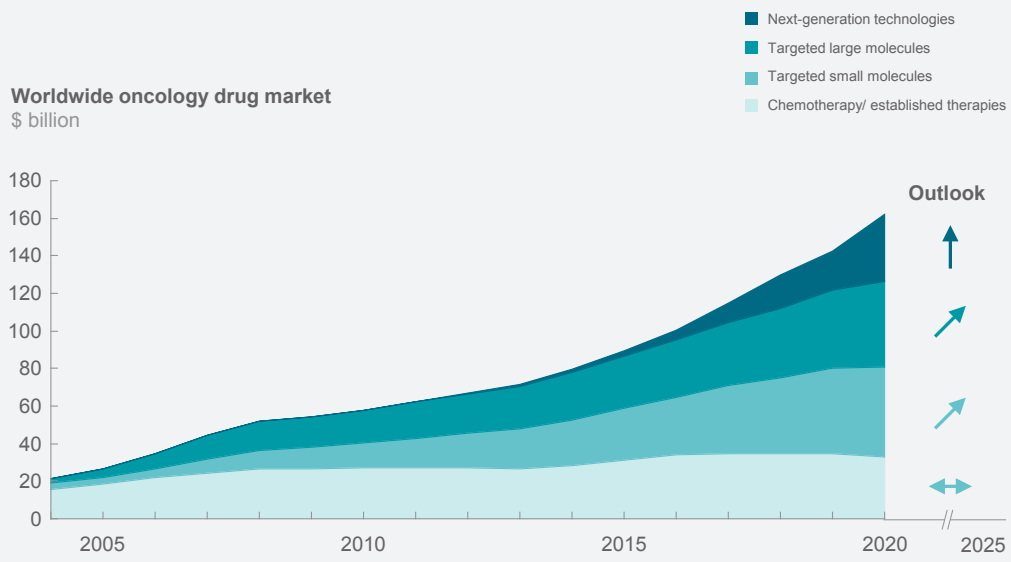
Opportunities from the new wave of innovation

According to consensus forecasts and our own research, the new wave of therapies could add up to 20 percent in market value over the next five years, potentially increasing the size of the oncology market in 2020 to $160 billion dollars (Exhibit 6). These technologies create four primary opportunities to improving cancer care for patients: earlier detection, new treatment strategies, personalization, and improved monitoring.

Exhibit 6

Next-generation technologies will further drive market growth

Market evolution of global oncology



Source: Analyst reports; Cowen Group; EvaluatePharma® 2015

Earlier detection

An ongoing drop in gene-sequencing costs, combined with a rise in capacity, makes it easier to obtain genetic information and fuel the adoption of precision medicine. Recent advances in liquid biopsy provide a further push for precision medicine by offering a minimally invasive method of measuring circulating tumor DNA and circulating tumor cells. This opens up an opportunity to diagnose cancer earlier, such as during a routine annual checkup when a patient is still asymptomatic. Illumina created Grail earlier this year to bring this concept to market, and other leaders in the sequencing field are working on this method. If successful, early detection may improve prognosis and shift significant value in healthcare.

New ways to treat

The introduction of biologics in the 1990s opened up new opportunities compared to small molecules, such as increased specificity and less frequent administration. Looking ahead, novel modalities such as advanced antibody constructs, cell therapies, nucleic-acid therapies, and cancer vaccines will create new avenues for treatment. Immunotherapies continue to make headlines, especially when used in combination. Yet significant unmet needs remain for the majority of patients who do not achieve a durable response with PD-1 or PD-L1. New therapies based on other costimulatory or checkpoint-inhibition targets are being tested as monotherapies or in combination with PD-1/PD-L1 therapies (for example, LAG-3, TIM-3, and OX40).

Preliminary results from cell therapies such as CAR-T demonstrate impressive efficacy for B-cell malignancies like relapsed and refractory acute lymphoblastic leukemia, which have previously been hard to treat. The second and third generations of CAR-T therapies are increasingly sophisticated, with built-in "activation" and "kill" switches to further improve specificity, safety, and amplification. However, recent setbacks due to adverse events have raised new doubts about leading programs in the pipeline. More broadly, the jury is still out on whether cell therapies can be as effective against solid tumors.

CRISPR is a high-precision gene-editing tool with the potential to provide a permanent cure and is already popular in preclinical research. The most advanced clinical applications of CRISPR focus on its use as an enabler of cell therapies (for example, an Intellia Therapeutics and Novartis collaboration[1]) or for select sites such as the liver, blood, and eye (for example, a Bayer and CRISPR Therapeutics collaboration[2] and an Intellia Therapeutics and Regeneron collaboration[3]). CRISPR may also be used to edit out T-cell receptors or major histocompatibility complexes to minimize immunogenic potential in allogeneic transplantation.

RNA therapeutics (mRNA, siRNA, and miRNA) provide new tools against targets that are difficult to treat with small molecules and biologics. These include transient silencing of transcription, producing intracellular or cell-surface proteins, and supplementing down-regulated or missing proteins. Several companies are already working on cancer therapies, including Moderna Therapeutics' Onkaido Therapeutics and Silence Therapeutics. The first products are likely to focus on several easy targets, such as the liver and blood, or on indications that permit intratumoral injection.

Personalization

Many new technologies enable further personalization of treatments. Improved diagnostics offer opportunities to stratify patients and monitor treatment response in order to fine-tune treatment regimens based on each patient's condition and circumstances.

Beyond finding the right drug at the right dose for the right patient at the right time, the next step in personalization is to tailor therapies based on a deeper understanding of biology.

1 "Novartis collaborates with Intellia Therapeutics and Caribou Biosciences to explore making medicines and drug discovery tools with CRISPR genome editing technology," Novartis, January 7, 2015, novartis.com.

2 "Bayer and CRISPR Therapeutics AG join forces to discover, develop and commercialize potential cures for serious genetic diseases," Bayer, December 12, 2015, bayer.com.

3 "Regeneron and Intellia Therapeutics announce collaboration to discover and develop CRISPR/Cas therapeutics," PR Newswire, April 11, 2016, prnewswire.com.

Examples include cell therapies, neoantigens, and the cancer microbiome. Moderna Therapeutics recently announced a collaboration with Merck to create personalized mRNA-based vaccines in conjunction with checkpoint inhibitors.[4] Other companies, such as Advaxis, Gritstone Oncology, and Neon Therapeutics are working on additional neoantigen-based approaches. It is still too early to know the full potential of neoantigen and microbiome approaches, but they may open up opportunities for indications where driver mutations are not available or not "druggable" by current modalities.

Improved monitoring

Easier access to sequencing and other biomarker technologies creates opportunities to monitor disease state and therapeutic response in a more nuanced way. That, together with better integration with electronic medical records and real-time decision support, will make information more accessible to physicians, building critical mass and enabling adoption. Syapse developed a digital platform that integrates genomic and clinical data, and works with integrated health systems to roll out precision-oncology programs at scale across community hospitals. Flatiron and others are exploring parallel avenues. Similarly, IBM Watson is working with the US Department of Veterans Affairs to broaden access to precision medicine[5].

Liquid biopsy will enable further monitoring and has two inherent advantages: lower costs and risks compared with a standard biopsy and fewer sampling issues. Its less invasive nature may increase adoption in genomic evaluation of less accessible tumors, assessment of response over time, and tracking of minimal residual disease.

Several leading companies are already offering personalized biopsy products, such as Foundation Medicine's FoundationACT, Genomic Health's Oncotype SEQ Liquid Select,

4 "Moderna announces license and collaboration agreement with Merck to develop messenger RNA-based antiviral vaccines and passive immunity therapies," Moderna Therapeutics, January 13, 2015, modernatx.com.

5 "US Department of Veterans Affairs Enlists IBM's Watson in the war on cancer," IBM, June 29, 2016, ibm.com.

Challenges for the new wave of innovation

The new wave of innovation brings with it challenges that must be overcome to fundamentally change the practice of oncology at scale. These barriers to change are related to regulation, reimbursement, knowledge, technical issues, drug development, and healthcare systems.

Regulatory and reimbursement barriers

Regulators and payors must embrace a much faster pace of innovation that is more complex than before, specifically in the form of combination therapies and individualized treatments for which each batch of product is different, as in cell therapies. Regulators need to grapple with this complexity and establish clear guidance on the regulatory standards for a platform versus individual treatments, as well as which departments take responsibility for which combinations. The rising cost of therapies (for example, from combination or curative therapies) is becoming a real concern for payors, especially when therapies may only work for a subset of the population, as is the case with checkpoint inhibitors. As discussed earlier, value-based approaches are being developed that will affect the reimbursement and adoption of these therapies. Two recent examples from outside oncology include Eli Lilly's Trulicity for diabetes and Novartis's Entresto for heart failure.

Knowledge barriers

A greater ability to measure biomarkers allows us to understand the dynamics of disease progression and treatment response. This also places more demand on our ability to interpret the results and translate them into action. Analytics based on big data and deep learning are beginning to help make sense of evidence accumulated from clinical trials, observational studies, and case reports and to guide the use of new therapies.

Technical barriers

The key technical barrier for novel therapeutic modalities will be targeted delivery. In terms of diagnostics, the key barrier is operational consistency to achieve sufficient robustness and sensitivity under different real-life conditions in multiple sites. Standardization of protocols and training to ensure the right skill sets will be required.

Development barriers

Patient recruitment will become increasingly challenging. Recruitment for indications of high incidence is difficult because of the number of trials conducted in parallel, creating fierce competition for patients. Smaller niche populations are also challenging, as a network of institutions may be required to recruit sufficient patients. Basket and umbrella trial designs may be one solution to finding the right patients for the right trials, but they will require extensive planning and collaboration.

System barriers

Fragmentation of healthcare systems adds complexity to the practical rollout of precision medicine. Today, significant differences remain between clinical practice at academic medical centers and at community hospitals. In the United States, these differences are diminishing, partly because of consolidation of oncology practices by integrated health networks and partly thanks to new companies (for example, Flatiron Health, Foundation Medicine, IBM Watson, NantHealth, and Syapse) that streamline oncology work flows, combine genomic information and electronic medical records, and translate these data into clear actionable reports. Any fragmentation at the systems level will set an upper limit on how fast change can be implemented.

Oncology in 2025

Given these trends, how might oncology look in 2025? (See sidebar opposite, “How might cancer care look in 2025?”)

Progress will be made in an overall shift toward an outcome-focused approach to cancer care. Innovation will continue to drive oncology onward, with greater emphasis on combinations and new therapeutic modalities that truly drive a step change in outcome. Some of these therapies may even be curative at some point and will require new innovation models in pharmaceutical and biotech companies, as well as new reimbursement models (such as installment).

On the systems side, different sources of healthcare information will be connected. Innovative companies will make progress in mining the information to gain more nuanced insights to optimize outcome. Physicians will use real-time decision-support systems to access the latest information. A broader range of information sources will be available, from liquid biopsies to connected health (that is, wearables and point-of-care diagnostics). By 2025, early detection and residual disease monitoring may be more common, resulting in a substantial impact on clinical outcome by catching disease at an early stage or with a lower burden.

Regulators will play a central partner role in charting the way ahead. Payors and integrated health systems will be active in shaping care pathways, as many of them will also become significant owners of real-world data.

■ ■ ■

The next years in oncology will be an exciting period that will see a new wave of innovation. At the same time, the competitive landscape will become more intense. Healthcare information will be better connected. There will be a greater requirement to demonstrate value and improved outcomes. Leaders in pharmaceuticals, diagnostics, healthcare systems, payors, and regulators must make critical decisions now in order to make the right investments and build the right capabilities to proactively shape the change and to be well positioned to capture the new value resulting from this rapid evolution.

How might cancer care look in 2025?

A 35-year-old patient lives in a rural area a hundred miles from a city. He visits a nearby clinic for his annual checkup. A doctor accesses his electronic medical record, downloads the latest information from the patient's smart watch, and conducts several routine physical tests. All looks normal. The man is sent for blood tests and waits for the results.

After thirty minutes, the doctor sees the patient to explain that the rapid diagnostic test for circulating tumor DNA (ctDNA) has detected early markers of esophageal cancer. Luckily, since the cancer is diagnosed early, the prognosis is good. The doctor wants further tests at a nearby specialist biopsy center. An app on the patient's smartphone finds available time slots, confirms health-insurance coverage, and schedules a visit at the specialist biopsy center within two days.

The patient visits the specialist biopsy center, by which time the blood tests from earlier have undergone further testing using a full panel of 150 ctDNA markers to characterize a range of genetic variations, including point mutations, amplifications, and fusions. All of his medical information is available to the specialist biopsy center. Another doctor performs an endoscopy and identifies a small lump, which is confirmed as cancer on biopsy. This positive finding automatically triggers scheduling of follow-up surgery three days later. In the meantime, the biopsy is sent to a personalized biopsy company that tests tissue biopsies for 200 neoantigens, surface markers, and other tumor markers.

Results from the tissue biopsy are returned in time for surgery. They define a specific and personalized fingerprint of tumor markers. These are combined with an algorithm provided by a big data company, compared with samples from millions of other people, and evaluated for an optimal therapeutic adjuvant regimen. A decision-support system informs the doctors about the best course of treatment for this particular patient, which is surgery and adjuvant combination treatment with a personalized immuno-oncology therapy and a targeted therapy.

The treatment is explained to the patient, who is able to find additional information online and from patient support groups that he is enrolled in by his clinic. The patient undergoes successful surgery to remove the primary tumor, followed by several rounds of adjuvant therapy.

Postoperatively, the patient's smart watch monitors his daily activity and provides his treatment team with insight into his well-being, including level of physical activity, walking speed, and amount of rest. His information is fed into a machine-learning algorithm that compares his well-being with similar patients and makes recommendations to adjust his treatment, diet, and activity programs (for example, yoga and hikes).

Liquid biopsy is used for monthly monitoring of his response and any residual disease. He is able to provide the liquid biopsy samples at home via a small finger prick, and a home reader sends raw data for processing and analysis. He receives any peer support that he needs in person from support groups and from online communities.

Twelve months later, the patient remains cancer free.

About the authors

About the authors

Björn Albrecht is a partner in McKinsey's London office, **Philippe Menu** is an associate partner in the Geneva office, **Jeff Tsao** is a consultant in the Boston office, and **Kevin Webster** is a consultant in the San Francisco office.

About the McKinsey Cancer Center

The McKinsey Cancer Center is an oncology-focused center of excellence that serves a broad spectrum of clients, including biotechnology and pharmaceutical companies, health systems, payors, and regulatory/health authorities, on a range of topics from R&D to commercialization. The center comprises an advisory board with preeminent business and scientific leaders in the field, dedicated oncology experts, consultants with relevant scientific and clinical training, and tailored methodologies and tools. The center also convenes leaders at the annual meeting of the American Society of Clinical Oncology.

McKinsey Cancer Center
September 2016

Designby Visual Media Europe
www.mckinsey.com